REMARKS

I. Amendments

Claims 1-10 and 17-28 are canceled. New claims 35-46 are being added. The newly added claims do not add or constitute new matter and are supported by the application as originally filed. More particularly, support for claims 35-41 may be found, for example, at page 2, lines 19-22, page 3, lines 1-15, page 6, lines 30-31, page 11, line 7 through page 15, line 13, page 26, lines 3-7 and page 53, line 15 through page 54, line 2 of the specification. Support for claims 42-44 may be found, for example, at page 8, line 28 through page 11, line 5, and page 53, line 15 through page 54, line 2 of the specification. Additionally, support for claims 45-46 may be found, for example, at page 11, lines 8-21, of the specification.

Amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later-filed divisional, continuation or continuation-in-part application.

Upon entry of the amendments, claims 35-46 are pending in the instant application.

II. Rejections

A. Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 8-10 and 17-28 under 35 U.S.C. § 112, first paragraph, asserting that the specification does not enable one skilled in the art to make the invention commensurate with the scope of the claims. Applicant respectfully traverses this rejection. In view of the cancellation of these claims, the recitations of the newly added claims and the following discussion, the Examiner's rejections under 35 U.S.C. § 112, first paragraph, are either moot or demonstrated to be inappropriate.

The Examiner asserts that the specification presents hot plate data for only two pairs of mice, and that one pair of mice appears to have similar latencies. The Examiner further asserts that the phenotype appears inconsistent between the two pairs of wild-type and knockout mice. Applicant respectfully disagrees and points out that the Examiner's assertions are inaccurate. Applicant draws the Examiner's attention to the column labeled "count" under "Hot Plate" in

Table 1 of the instant application. This column refers to the number of mice of each genotype and generation subjected to the Hot Plate test. Consequently, the Examiner's assertion that the specification provides data for only two pair of mice is incorrect. Further, Examiner's bald opinion that the latencies are "very similar" is both inappropriate and inaccurate. In fact, as shown by the data provided in Table 1, both the F2N0 and the F2N1 generations of knockout mice display a decreased latency to respond to a thermal stimulus, relative to wild-type mice of the same generation, with the F2N1 knockout mice showing a more marked decrease in response latency. Therefore, Applicant respectfully disagrees with the Examiner's assertion that the phenotype is inconsistent between the two pairs of wild-type and knockout mice.

Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 112, first paragraph. Applicant submits that new claims 35-46 fully meet the requirements and are patentable under 35 U.S.C. § 112, first paragraph.

B. Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-4, 9, 10 and 28 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicant respectfully traverses this rejection.

The Examiner asserts that the arrangement of the target construct is unclear. Applicant submits that the new claims clearly set forth the relative arrangement of the elements of the targeting construct, rendering the Examiner's rejection moot.

The Examiner further asserts that it is not clear what the word "providing" encompasses in claims 3 and 4. Applicant respectfully disagrees. The term "providing" is well known in the art and therefore one of ordinary skill in the art would know what the term "providing" encompasses.

In rejecting claim 2, the Examiner asserts that it is unclear what the term "screening marker" encompasses, and how a "screening marker" differs from a "selection marker". Applicant respectfully disagrees. The definition and distinction between the terms "selection marker" and "screening marker" are clearly set forth at, for example, pages 12 and 13 of the instant specification. However, the current claims do not recite either "selection marker" or "screening marker" and therefore render the Examiner's rejection moot.

Further, the Examiner asserts that the word "derived" renders claims indefinite.

Applicant respectfully disagrees. As can be found, for example, on page 2, lines 19-21 of the instant specification, the term "derived" is clearly defined and therefore not indefinite. Further, one of ordinary skill in the art would know to what the term "derived", in the context of cells and tissues "derived" from a transgenic mouse, relates. In any case, the current claims do not use the term "derived" and therefore render the Examiner's rejection moot.

Applicant submits that new claims 35-46 are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph.

C. Rejection under 35 U.S.C. § 103

Claims 1-8 and 10 stood rejected as being unpatentable under 35 U.S.C. § 103(a) based upon the teachings of Manes *et al.*, 1990, *Genomics* 8:541-554 ("Manes") and Mansour *et al.*, 1988, *Nature* 336(24):348-352 ("Mansour"). Applicant respectfully traverses this rejection.

Mansour describes a general approach for isolating embryonic stem cells containing targeted mutation in any gene, provided that a cloned fragment of the gene is available. Specifically, Mansour teaches the targeted disruption of the *hprt* gene and the proto-oncogene *int*-2 in mouse embryo-derived stem cells by homologous recombination using targeting constructs pRV9.1/TK and pINT-2-N/TK respectively. The Examiner concedes, however, that Mansour does not teach how to make an intestinal alkaline phoshpatase gene targeting construct and knockout mouse.

Manes merely teaches the identification and cloning of a mouse intestinal alkaline phosphatase gene.

As a basis of the obviousness rejection under 35 U.S.C. § 103, the Examiner asserts that the ordinary artisan would have been motivated to knock out the expression of the intestinal alkaline phosphatase gene in a mouse to study the function of this gene in the context of the alkaline phosphatase family, and understanding its structure-function relationship in evolutionary processes, as suggested by Manes. The Examiner further asserts that the ordinary artisan would have had a reasonable expectation of success because of the teachings of Mansour and Manes. The Applicant respectfully disagrees.

In order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must meet three basic criteria:

1. there must be some motivation or suggestion to modify the reference or combine reference teachings;
2. there must be a reasonable expectation of success; and
3. the prior art references must teach or suggest all the claim limitations.

There is no teaching in Manes that suggests the desirability of knocking out the intestinal alkaline phosphatase gene. On page 9 of the Office Action, the Examiner cites Manes as teaching that that the alkaline phosphatase family of genes represents a system suitable for approaching questions concerning the evolution of tissue specific genes and their restricted expression, the mechanisms underlying genetic polymorphism, as well as the progressive change in the catalytic properties and function of enzymes in the context of an isozyme family.

The suggestion by Manes that the alkaline phosphatase family of genes may be used for studying the evolution, expression, genetic polymorphism, changes in catalytic properties and function of enzymes is not sufficient motivation to modify Manes or combine Manes with Mansour to produce an intestinal alkaline phosphatase gene knockout mouse, and thus to establish a *prima facie* case of obviousness. The mere fact that a reference can be modified does not render the invention obvious unless the prior art also suggests the desirability of the modification. In the instant case, Manes does not, in any way, suggest the desirability of knocking out the intestinal alkaline phosphatase gene, even as a way to further elucidate the role the gene may play in alkaline phosphatase function.

The Examiner asserts that the ordinary artisan would have had a reasonable expectation of success because of the teachings of Mansour, who teaches a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Manes, who teaches the coding sequence of the mouse intestinal alkaline phosphatase gene. However, when combining references, the Examiner must show some teaching, motivation or suggestion to combine the references. The mere fact that the references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. Further, the fact that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. Finally, the level of skill in the art cannot be relied upon to provide the suggestion to combine references. In the instant case, there is no motivation to combine the teachings of Mansour with Manes to achieve

the claimed invention. Mansour teaches a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a gene. There is no teaching or suggestion in Mansour as to the desirability of a targeted disruption of an intestinal alkaline phosphase gene. Similarly, Manes teaches the coding sequence of the intestinal alkaline phosphatase gene. However, there is no suggestion in Manes to create a targeted disruption of an intestinal alkaline phosphatase gene.

Finally, to establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. However, neither Mansour nor Manes, alone or in combination, teach all of the limitations of the instant claims. For example, neither Mansour nor Manes teach or suggest a transgenic mouse with a disrupted intestinal alkaline phosphatase gene exhibiting a phenotype, particularly not a nociceptive abnormality or abnormal activity level, or methods of making such a mouse, which inventions are the subject of the pending claims.

Applicant submits that new claims 35-46 are not obvious in view of the sole or combined teachings of Manes or Mansour and respectfully requests withdrawal of the rejection under 35 U.S.C. § 103.

It is believed that the claims are in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-733.

Respectfully submitted,

Date: January 11, 2003

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Enclosures